2ND ANNUAL
ADVANCED HEPATOLOGY EDUCATIONAL SUMMIT
FOR 3RD YEAR GI FELLOWS

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Provided by:
NASH: Current Approach and When Will New Treatment Options Be Available?

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Faculty Disclosures

- **Research Support:** BMS, Gilead, Intercept.

- **Consultant:** BMS, Gilead, Intercept, NovoNordisk, Siemens, Terns, Viking.
NASH in the Context of the Spectrum of NAFLD

NAFLD

- Steatosis in >5% of hepatocytes
- NASH requires specific pathologic criteria
- Exclusion of secondary causes and AFLD

NAFL

- Pure steatosis
- Steatosis and mild lobular inflammation

Early
F1 fibrosis

Fibrotic
F2 fibrosis

NASH

Fibrotic
F3 fibrosis

Cirrhotic
F4 fibrosis

HCC

The Global Prevalence of NAFLD and NASH

Prevalence of NAFLD and NASH

- **North America**: 24.1%
- **Europe**: 23.7%
- **Asia**: 27.4%
- **Middle East**: 31.8%
- **South America**: 30.5%
- **Africa**: 13.5%

*In T2DM (US)*
- **North America**: 51.8%
- **Europe**: 68.0%
- **Middle East**: 31.8%
- **Africa**: 30.4%

*Worldwide prevalence of NAFLD is 25%
*Worldwide prevalence of NAFLD among people with T2DM is 55.5%

Prevalence of NASH in general population is between 1.5–6.5%
Prevalence of NASH among T2DM is 37.3% (24.7-50.0%)

T2DM, type 2 diabetes mellitus.
The Global Prevalence of NAFLD in Children

Worldwide prevalence of NAFLD among Children is about 7-10%

- Prevalence is higher in boys and increases with higher BMI
- U.S. studies have revealed a 4-fold higher risk of hepatic steatosis in Hispanic, compared to non-Hispanic
- The prevalence of NAFLD in the US increased 2.7 fold from the late 1980’s to 2010

Clinical Outcomes: Natural History of NAFLD and NASH

The most common cause of death

Normal
Non-NASH 70-93%
NASH (7-30%)
NASH with fibrosis
NASH with advanced fibrosis
Cirrhotic HCC
Non-cirrhotic HCC

0.592% per year
2.3% per year

Clinical Outcomes: Natural History of NAFLD and NASH

HCC, hepatocellular carcinoma.
Evidence Supporting Adverse Clinical Outcomes in NASH

NASH Denotes Progressive Disease

Components of MS Predicts Mortality-NHANES III

Stage of Fibrosis Predicts Mortality

HCC and NAFLD- SEER 2004–2009

Growing LT Due to NASH in the US

LT Due to NASH-related HCC


Changes in CLD Mortality National Center for Health Statistics Mortality data

Changes in Age-standardized Incidence and Death Rates Related to Cirrhosis and Liver Cancer According to Etiology of Liver Disease


<table>
<thead>
<tr>
<th>Etiology of Liver Disease</th>
<th>Global</th>
<th>Australia</th>
<th>High-income Asia Pacific</th>
<th>High-income North America</th>
<th>Southern Latin America</th>
<th>Western Europe</th>
<th>Central Asia</th>
<th>Eastern Europe</th>
<th>South Asia</th>
<th>East Asia</th>
<th>Southeast Asia</th>
<th>Oceania</th>
<th>Caribbean</th>
<th>Andean Latin America</th>
<th>Central Latin America</th>
<th>Tropical Latin America</th>
<th>North Africa and Middle East</th>
<th>Central Sub-Saharan Africa</th>
<th>Eastern Sub-Saharan Africa</th>
<th>Southern Sub-Saharan Africa</th>
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<th>High SDF</th>
<th>High-middle SDF</th>
<th>Low SDF</th>
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<tbody>
<tr>
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<tr>
<td>Liver cancer due to Other causes</td>
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<td>Liver cancer due to HAI</td>
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<tr>
<td>Liver cancer due to Others</td>
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<td>0.000</td>
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</tbody>
</table>

**Trends in Mortality Rates (2012-2017)**

| Etiology of Liver Disease | Global | Australia | High-income Asia Pacific | High-income North America | Southern Latin America | Western Europe | Central Asia | Eastern Europe | South Asia | East Asia | Southeast Asia | Oceania | Caribbean | Andean Latin America | Central Latin America | Tropical Latin America | North Africa and Middle East | Central Sub-Saharan Africa | Eastern Sub-Saharan Africa | Southern Sub-Saharan Africa | Western Sub-Saharan Africa | High SDF | High-middle SDF | Low SDF |
|--------------------------|--------|-----------|--------------------------|--------------------------|------------------------|-----------------|------------|--------------|-----------|-----------|---------------|--------|---------|----------------|----------------|----------------|-----------------|-----------------|----------------|----------------|----------------|----------------|----------------|
| Liver cancer due to HCV  | 0.000  | 0.000     | 0.000                    | 0.000                    | 0.000                  | 0.000           | 0.000      | 0.000         | 0.000    | 0.000    | 0.000         | 0.000  | 0.000   | 0.000          | 0.000           | 0.000          | 0.000            | 0.000           | 0.000          | 0.000          | 0.000          | 0.000          |
| Liver cancer due to HBV  | 0.000  | 0.000     | 0.000                    | 0.000                    | 0.000                  | 0.000           | 0.000      | 0.000         | 0.000    | 0.000    | 0.000         | 0.000  | 0.000   | 0.000          | 0.000           | 0.000          | 0.000            | 0.000           | 0.000          | 0.000          | 0.000          | 0.000          |
| Liver cancer due to HAA   | 0.000  | 0.000     | 0.000                    | 0.000                    | 0.000                  | 0.000           | 0.000      | 0.000         | 0.000    | 0.000    | 0.000         | 0.000  | 0.000   | 0.000          | 0.000           | 0.000          | 0.000            | 0.000           | 0.000          | 0.000          | 0.000          | 0.000          |
| Liver cancer due to Other causes | 0.000 | 0.000     | 0.000                    | 0.000                    | 0.000                  | 0.000           | 0.000      | 0.000         | 0.000    | 0.000    | 0.000         | 0.000  | 0.000   | 0.000          | 0.000           | 0.000          | 0.000            | 0.000           | 0.000          | 0.000          | 0.000          | 0.000          |
| Liver cancer due to HAI   | 0.000  | 0.000     | 0.000                    | 0.000                    | 0.000                  | 0.000           | 0.000      | 0.000         | 0.000    | 0.000    | 0.000         | 0.000  | 0.000   | 0.000          | 0.000           | 0.000          | 0.000            | 0.000           | 0.000          | 0.000          | 0.000          | 0.000          |
| Liver cancer due to Others | 0.000 | 0.000     | 0.000                    | 0.000                    | 0.000                  | 0.000           | 0.000      | 0.000         | 0.000    | 0.000    | 0.000         | 0.000  | 0.000   | 0.000          | 0.000           | 0.000          | 0.000            | 0.000           | 0.000          | 0.000          | 0.000          | 0.000          |

Evidence Supporting Adverse Clinical Outcomes, Patient Reported Outcomes and Economic Outcomes in NASH

Future Estimates of Disease Burden

- 20% of NAFLD is NASH
- 27% NAFLD will be NASH

Cases of F3 due to NASH
- 2 M in 2015
- 4.5 M in 2030

Cases of F4 due to NASH
- 1.3 M in 2015
- 3.5 M in 2030

By 2030, there are projected to be nearly 800,000 excess liver deaths in the US

Incident decompensated cirrhosis +168%

Patient Reported Outcomes in NASH

- 6.65 million adults with NASH
- 688,000 advanced NASH
- $222.6 billion in lifetime direct costs of total NASH population
- $95.4 billion in lifetime direct costs of advanced NAS

Economic Burden of NASH

NAFLD Is Part of a Multisystem Disorder

- Vascular disease
- Chronic kidney disease
- Osteoarthritis
- Cardiac disease
- Cerebrovascular disease
- Diabetes
- Gallstone disease
- Obstructive sleep apnea
- Polycystic ovary syndrome
- Malignancy


<table>
<thead>
<tr>
<th>Site</th>
<th>Fold increase*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liver</td>
<td>4.0</td>
</tr>
<tr>
<td>Stomach</td>
<td>3.5</td>
</tr>
<tr>
<td>Lung</td>
<td>2.0</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Author</th>
<th>CVD Death</th>
</tr>
</thead>
<tbody>
<tr>
<td>Angulo, 2015</td>
<td>38.3%</td>
</tr>
<tr>
<td>Söderberg, 2010</td>
<td>30%</td>
</tr>
<tr>
<td>Ekstedt, 2006</td>
<td>16%</td>
</tr>
<tr>
<td>Dam-Larsen, 2009</td>
<td>38%</td>
</tr>
<tr>
<td>Rafiq, 2009</td>
<td>12.7%</td>
</tr>
</tbody>
</table>
NASH Is the Consequence of Complex Pathogenesis

DAMP, danger-associated molecular patterns; ECM, extracellular matrix; IL-1β, interleukin-1beta; PAMP, pathogen-associated molecular patterns; PDGF, platelet-derived growth factor; TGF-β, transforming growth factor beta; TNF, tumor necrosis factor; TNF-β, tumor necrosis factor-beta.

Diagnostic Modalities for NAFLD, NASH and Fibrosis

• **Invasive Modalities:**
  - Histology (liver biopsy is the imperfect gold standard)

• **Non-invasive Modalities:**
  - International efforts to find NITs: LITMUS (EU) and NIMBLE (US)

### Clinical/lab tests
- NAFLD fibrosis score
- FIB-4 index
- BARD score
- AST: ALT ratio
- AST: platelet ratio index
- Hepascore®
- FibroTest®
- FibroMeter®
- Fatty liver index
- Index of NASH

### Imaging
- Ultrasound
- Computer tomography
- Magnetic resonance imaging
- Magnetic resonance spectroscopy
- Transient elastography
- Acoustic radiation force impulse
- Magnetic resonance elastography

### Biomarkers
- Hyaluronic acid
- Fucosylated haptoglobin (Fuc-Hpt)
- Macroglobulin-2 binding protein (Mac-2bp)
- Fuc-Hpt + Mac-2bp
- ELF score
- FIBROSpect®
- PRO C3

**Abbreviations:**
ALT, alanine aminotransferase; AST, aspartate aminotransferase; ELF, enhanced liver fibrosis; MRI, magnetic resonance imaging.

### Disadvantages of biopsies

1. Sampling variability
2. Pain and infection
3. Death
4. Perforation, bleeding
5. Impractical for population
6. Costs

### Liver Biopsy: The Imperfect Gold Standard

### Non-invasive Tests for NASH

<table>
<thead>
<tr>
<th>Study</th>
<th>Performance of Clinical Algorithms</th>
<th>AUC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ratziu et al. BAAT (≥1) BMI, ALT, Age, TG</td>
<td>ND</td>
<td></td>
</tr>
<tr>
<td>Harrison et al. BARD (≥2) BMI, AST/ALT, DM</td>
<td>0.81</td>
<td></td>
</tr>
<tr>
<td>Cales et al. Glu, AST, PLT, Fer, Weight, Age</td>
<td>0.92</td>
<td></td>
</tr>
<tr>
<td>Feldstein et al. CK-18</td>
<td>0.83</td>
<td></td>
</tr>
<tr>
<td>Feldstein et al. CK-18, sFasL</td>
<td>0.93</td>
<td></td>
</tr>
<tr>
<td>Feldstein et al. oXNASH</td>
<td>0.83</td>
<td></td>
</tr>
<tr>
<td>(13-HODE/LA, age, BMI, AST)</td>
<td>0.83</td>
<td></td>
</tr>
<tr>
<td>Younossi et al. NASH Diagnostics</td>
<td>0.98</td>
<td></td>
</tr>
<tr>
<td>Poynard et al. Nash Test</td>
<td>0.79</td>
<td></td>
</tr>
<tr>
<td>Palekar et al. HA + Clinical model</td>
<td>0.76</td>
<td></td>
</tr>
<tr>
<td>Loomba et al. Lipidomic</td>
<td>1.00</td>
<td></td>
</tr>
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</table>

Large scale validation of these tests is lacking.
Can We Use Noninvasive to Estimate Liver Fibrosis? Commonly Used Fibrosis Scores

- **FIB-4 Index**:  
  - Originally developed to predict advanced fibrosis in HIV/HCV coinfection  
  - Subsequently studied in 541 patients with NAFLD (AUROC 0.80)

- **APRI**:
  - Meta-analysis of 40 studies  
  - The lower the APRI score (less than 0.5), the greater the negative predictive value (and ability to rule out cirrhosis) and the higher the value (greater than 1.5) the greater the positive predictive value (and ability to rule in cirrhosis).

- **NAFLD Fibrosis Score (NFS)**:
  - 733 NAFLD: 480 derivation; 253 validation  
  - Multivariate analysis (Age, hyperglycemia, BMI, platelet count, albumin, AST/ALT ratio) are independent predictors of advanced fibrosis

### FIB-4 Cutoff Value

<table>
<thead>
<tr>
<th>Stage</th>
<th>Cutoff Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>F0–F2</td>
<td>&lt;1.45</td>
</tr>
<tr>
<td>Indeterminate</td>
<td>1.45 to 3.25</td>
</tr>
<tr>
<td>F3–F4</td>
<td>&gt;3.25</td>
</tr>
</tbody>
</table>

### APRI

The lower the APRI score (<0.5), the greater the NPV (and ability to rule out cirrhosis) and the higher the value (>1.5) the greater the PPV (and ability to rule in cirrhosis).

### NFS Cutoff Value

<table>
<thead>
<tr>
<th>Stage</th>
<th>Cutoff Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>F0–F2</td>
<td>&lt;1.455</td>
</tr>
<tr>
<td>Indeterminate</td>
<td>-1.455 to 0.676</td>
</tr>
<tr>
<td>F3–F4</td>
<td>&gt;0.676</td>
</tr>
</tbody>
</table>

The Enhanced Liver Fibrosis Test (ELF)

Components

- Procollagen III N-terminal peptide (PIIINP)
- Hyaluronic acid (HA)
- Tissue inhibitor of metalloproteinase 1 (TIMP1)

<table>
<thead>
<tr>
<th>Fibrosis</th>
<th>ELF</th>
<th>S (%)</th>
<th>Sp (%)</th>
<th>PPV (%)</th>
<th>NPV (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Significant fibrosis ≥2</td>
<td>9.93</td>
<td>57</td>
<td>90</td>
<td>88</td>
<td>64</td>
</tr>
<tr>
<td></td>
<td>10.09</td>
<td>100</td>
<td>88</td>
<td>61</td>
<td>100</td>
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<td><strong>10.18</strong></td>
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<td>10.30</td>
<td>82</td>
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<td>100</td>
<td>97</td>
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<tr>
<td>Advanced fibrosis ≥3</td>
<td>10.51</td>
<td>100</td>
<td>98</td>
<td>80</td>
<td>100</td>
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<tr>
<td></td>
<td>10.78</td>
<td>50</td>
<td>99</td>
<td>80</td>
<td>96</td>
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<tr>
<td></td>
<td>11.56</td>
<td>25</td>
<td>100</td>
<td>100</td>
<td>95</td>
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</tbody>
</table>

- Patients with NASH and bridging fibrosis (n=219) or compensated cirrhosis (n=258) enrolled in two Phase 2b SIM studies were used to show that ELF can predict progression to cirrhosis and development of liver-related clinical events.
- Optimal threshold of baseline ELF: 9.76 (sensitivity 77%, specificity 66%)

## Technique

### Transient elastography (TE)
- **US**
  - **Liver stiffness** expressed in kPa; correlates with liver fibrosis stage
  - **Controlled Attenuation Parameter (CAP™)** expressed in dB/meter
  - Accurate in detecting advanced fibrosis
  - Predicts risk of decompensation
  - Correlates well with portal pressure
  - Most widely used

### Acoustic radiation force impulse (ARFI)
- **US**
  - Employs high intensity acoustic beam to mechanically excite tissue and monitor tissue displacement response
  - No need for an external compression
  - Degree of displacement is interpreted into degree of lightness and darkness

### Shear wave elastography (SWE)
- **US**
  - Shear waves are generated from acoustic pulses forced at five different tissue depth levels and SW velocity estimated by ultrafast Doppler-like acquisition of 5,000 frames/sec.
  - SW is converted to tissue stiffness as kilopascals

### Magnetic resonance elastography (MRE)
- **MR**
  - Most accurate of the imaging modalities
  - Costly, no point-of-care access
  - MRI Methods to Estimate Proton Density Fat Fraction
  - MRI-PDF shown to have high correlation to morphometric fat³

## Visualize liver

### Fibrosis Severity

<table>
<thead>
<tr>
<th>Without F3-F4 fibrosis</th>
<th>Median LSM (range)</th>
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<tbody>
<tr>
<td>6.6 kPa (5.3-8.9)</td>
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<table>
<thead>
<tr>
<th>With F3-F4 fibrosis</th>
<th>Median LSM (range)</th>
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<tr>
<td>14.4 kPa (12.1-24.3)</td>
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<table>
<thead>
<tr>
<th>Median Values</th>
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<tr>
<td>F0 6.93 kPa</td>
</tr>
<tr>
<td>F1 7.7 kPa</td>
</tr>
<tr>
<td>F2 9.6 kPa</td>
</tr>
<tr>
<td>F3 13.95 kPa</td>
</tr>
<tr>
<td>F4 23.73 kPa</td>
</tr>
</tbody>
</table>

### Stiffness cutoff: 3.63 kPa
- Sensitivity 0.86
- Specificity 0.91
AUC for advanced fibrosis: 0.924
Imaging Biomarkers: Which Test or Combination?

VCTE, ARFI, and SWE have limitations:
- Obesity
- Ascites
- Acute inflammation
- Cirrhosis

MRE improves upon all except
- Iron overload
- Acute inflammation

Combination of multiple Imaging and NITs may be part of the solution
- Baseline biopsies [ STELLAR 3 & 4, N=3202, 71% F3-F4]

### Combination of Non-invasive Biomarkers to Reduce Indeterminants

#### Single NIT with 2 cutoffs

High sensitivity cutpoint: 0.74
High specificity cutpoint: 0.78

Indeterminate: Need additional test

#### Sequential algorithms including 2 tests

High sensitivity cutpoint: 0.78
High specificity cutpoint: 0.78

Indeterminate: Need biopsy or other NIT

#### Sequential algorithms including 3 tests

High sensitivity cutpoint: 0.80
High specificity cutpoint: 0.80

Indeterminate: Need biopsy or other NIT

---

<table>
<thead>
<tr>
<th>Test</th>
<th>AUROC</th>
<th>F3-4 %</th>
<th>Cutoffs*</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PPV</th>
<th>NPV</th>
<th>Ind.</th>
<th>Misclass</th>
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</thead>
<tbody>
<tr>
<td>NFS n=385</td>
<td>0.74</td>
<td>79</td>
<td>&lt;1.11, 20.47</td>
<td>82 (77-85)</td>
<td>87 (79-93)</td>
<td>90 (96-98)</td>
<td>56 (41-64)</td>
<td>40 (35-44)</td>
<td>17 (14-21)</td>
</tr>
<tr>
<td>FIB-4 n=327</td>
<td>0.78</td>
<td>71</td>
<td>&lt;1.23, 22.1</td>
<td>83 (80-87)</td>
<td>89 (84-93)</td>
<td>95 (93-97)</td>
<td>60 (47-74)</td>
<td>52 (30-35)</td>
<td>15 (12-18)</td>
</tr>
<tr>
<td>ELF n=337</td>
<td>0.80</td>
<td>71</td>
<td>&lt;9.35, 20.47</td>
<td>85 (82-88)</td>
<td>85 (79-90)</td>
<td>93 (90-95)</td>
<td>71 (64-76)</td>
<td>29 (26-33)</td>
<td>15 (12-18)</td>
</tr>
<tr>
<td>LS by TE-kPa n=327</td>
<td>0.80</td>
<td>84</td>
<td>&lt;9.0, 14.03</td>
<td>88 (76-95)</td>
<td>82 (78-86)</td>
<td>94 (97-99)</td>
<td>49 (39-59)</td>
<td>25 (21-30)</td>
<td>17 (13-21)</td>
</tr>
</tbody>
</table>

---

<table>
<thead>
<tr>
<th>Test cutoffs</th>
<th>F3-4 %</th>
<th>% (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>FIB (1.23, 2.1)</td>
<td>71</td>
<td>(74-98)</td>
</tr>
<tr>
<td>ELF (9.8, 11.3)</td>
<td>71</td>
<td>(64-73)</td>
</tr>
<tr>
<td>FIB (1.3, 2.67)</td>
<td>71</td>
<td>(69-78)</td>
</tr>
<tr>
<td>FIB (1.23, 2.1)</td>
<td>71</td>
<td>(71-79)</td>
</tr>
<tr>
<td>FIB (1.3, 2.67)</td>
<td>71</td>
<td>(60-69)</td>
</tr>
</tbody>
</table>
Treatment for NAFLD and NASH

Multi-prong Approach to Manage Obesity

Public Health Interventions

Therapeutic Targets:
- Improving Hepatic Metabolism
- Improving insulin sensitivity
- Improving inflammation
- Improving fibrosis

Patient Target:
- NASH
- NASH with Advanced Fibrosis

Public Health Interventions

Therapeutic Targets:
- Improving Hepatic Metabolism
- Improving insulin sensitivity
- Improving inflammation
- Improving fibrosis

Patient Target:
- NASH
- NASH with Advanced Fibrosis

Public Health Interventions

Therapeutic Targets:
- Improving Hepatic Metabolism
- Improving insulin sensitivity
- Improving inflammation
- Improving fibrosis

Patient Target:
- NASH
- NASH with Advanced Fibrosis
### Probability of improving NASH components according to weight loss\(^1,2\)

52 weeks of lifestyle intervention

<table>
<thead>
<tr>
<th>% Weight Loss (WL)</th>
<th>5%</th>
<th>7%</th>
<th>10%</th>
</tr>
</thead>
<tbody>
<tr>
<td>NASH Resolution</td>
<td>10%</td>
<td>26%</td>
<td>64%</td>
</tr>
<tr>
<td>Fibrosis Regression(^a)</td>
<td>45%</td>
<td>38%</td>
<td>50%</td>
</tr>
<tr>
<td>Steatosis Improvement</td>
<td>35%</td>
<td>65%</td>
<td>76%</td>
</tr>
<tr>
<td>% Patients Achieving WL</td>
<td>70%</td>
<td>12%</td>
<td>9%</td>
</tr>
</tbody>
</table>

\(^a\) At least one stage.

### AASLD Guidance 2018

**Weight Loss and Exercise**

- **Weight loss**
  - 3%-5% to improve steatosis, but 7%-10% to improve the majority of the histologic features of NASH, including fibrosis

- **Sustainability of weight loss:**
  - Seven trials, total of 373 patients underwent weight loss programs 1 month to 1 year
  - 15% with “success”, most of these regain weight.
  - No strong evidence of sustained benefit.

- **Bariatric surgery and endoscopy**

**Weight loss can be effective but hard to achieve and sustain**

Moderate exercise may also be beneficial.
Pharmacologic Treatment for NAFLD and NASH
Currently, No Approved Drug!

<table>
<thead>
<tr>
<th>Not FDA Approved but AASLD Guidance Supports Use</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Pioglitazone</td>
</tr>
<tr>
<td>• Vitamin E</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Products of Significant Interest but Evidence is not Available</th>
</tr>
</thead>
<tbody>
<tr>
<td>• GLP-1 Agonist</td>
</tr>
<tr>
<td>• SGL2 Inhibitors</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Current Evidence Does not Support Efficacy for Treating NASH</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Caspase inhibitors</td>
</tr>
<tr>
<td>• Ursodeoxycholic acid</td>
</tr>
<tr>
<td>• Anti-obesity medications</td>
</tr>
<tr>
<td>• Betaine</td>
</tr>
<tr>
<td>• N-Acetyl-cysteine</td>
</tr>
<tr>
<td>• Lecithin</td>
</tr>
<tr>
<td>• Silymarin</td>
</tr>
<tr>
<td>• Beta-carotene</td>
</tr>
<tr>
<td>• Omega 3 Fatty Acid (Pufa, ‘Fish Oil’)</td>
</tr>
<tr>
<td>• Anti-TNF agents (Pentoxifylline)</td>
</tr>
<tr>
<td>• ACE inhibitors/ARBs</td>
</tr>
<tr>
<td>• Metformin</td>
</tr>
<tr>
<td>• Probiotics (VSL#3)</td>
</tr>
<tr>
<td>• Lipid Lowering agents (statins)</td>
</tr>
</tbody>
</table>
RCT, randomized controlled trial.

Heterogeneity: $\tau^2=0.00$; $\chi^2=2.39$, $df=4$ ($P=0.66$); $I^2=0\%$.

Test for overall effect: $z=2.72$ ($P=0.007$).

N=101 NASH with prediabetes or T2DM. All participants were placed on a 500 kcal/d deficit diet and randomized to placebo or pioglitazone 30 mg/day (titrated to 45 mg/d after 2 months) for 18 months.


<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Weight, %</th>
<th>Odds Ratio M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aithal et al, 2009</td>
<td>13.2</td>
<td>7.49 (0.37-151.50)</td>
</tr>
<tr>
<td>Belfort et al, 2006</td>
<td>14.0</td>
<td>16.54 (0.89-308.98)</td>
</tr>
<tr>
<td>Cusi et al, 2016</td>
<td>13.8</td>
<td>9.97 (0.52-190.16)</td>
</tr>
<tr>
<td>Sanyal et al, 2004</td>
<td>14.0</td>
<td>1.00 (0.05-18.57)</td>
</tr>
<tr>
<td>Sanyal et al, 2010</td>
<td>45.0</td>
<td>3.28 (0.64-16.78)</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>100.0</td>
<td>4.53 (1.52-13.52)</td>
</tr>
</tbody>
</table>

- Potential AEs: bone loss, diastolic dysfunction, weight gain?
- Pioglitazone-AASLD 2018
  - Pioglitazone improves liver histology in patients with and without T2DM with biopsy-proven NASH
  - Risks and benefits should be discussed with each patient
  - Should not be used for NAFLD without biopsy-proven NASH

Current Management of NASH
Vitamin E

<table>
<thead>
<tr>
<th>Authors</th>
<th>N</th>
<th>Dose</th>
<th>Comparators</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arendt</td>
<td>80</td>
<td>1000 IU/d</td>
<td>Placebo</td>
<td>Improved steatosis (assessed by CT scan) vs placebo</td>
</tr>
<tr>
<td>Sanyal</td>
<td>247</td>
<td>800 IU/d</td>
<td>Pioglitazone, placebo</td>
<td>Improved steatosis, inflammation, and ballooning vs placebo</td>
</tr>
<tr>
<td>Lavine</td>
<td>173</td>
<td>800 IU/d</td>
<td>Metformin, placebo</td>
<td>Improved steatohepatitis and ballooning vs placebo</td>
</tr>
<tr>
<td>Harrison</td>
<td>45</td>
<td>1000 IU/d</td>
<td>Placebo</td>
<td>Improved fibrosis vs baseline</td>
</tr>
</tbody>
</table>

**Vitamin E in Patients with Advanced Fibrosis**

- 236 patients with NASH and bridging fibrosis or cirrhosis
- 90 patients took vitamin E 800 IU/day for > 2 years
- 90 patients did not take vitamin E

**First Event of Hepatic Decompensation**

**Transplant-Free Survival**

**AASLD Guidance document:**
- Vitamin E: At 800 IU/day improves histology in nondiabetic with NASH
- Risks and benefits should be discussed
- Not recommended for NASH in diabetic patients, NAFLD without a liver biopsy, NASH cirrhosis, or cryptogenic cirrhosis

Current Management of NASH
GLP-1 Agonists

83% of patients had weight loss >5%

GLP-1RAs-AASLD 2018
- It is premature to consider GLP-1 agonists to specifically treat liver disease in patients with NAFLD or NASH

If Standard Treatment Is Unsuccessful, What Future Options Exist?
Regimens in Phase 3 Clinical Trials for Treatment of NASH

**MARKETED**

- **Cenicriviroc** (CCR2/CCR5)
  - Met NASH endpoint in Phase 2 Golden-505
  - Phase 3 AURORA is on going

- **Obeticholic acid** (FXR)
  - Met primary endpoint in phase 2 FLINT
  - Met fibrosis endpoint in phase 3 REGENERATE

- **Selonsertib** (ASK-1)
  - Did not meet Fibrosis endpoint in cirrhotics (STELLAR 4)
  - Did not meet Fibrosis endpoint in F3 NASH (STELLAR 3)

**PHASE 3**

- Met only fibrosis improvement in Phase 2 CENTAUR
- Phase 3 AURORA is on going

**PHASE 2**

- **Elafibranor** (PPARα/σ)
  - Met NASH endpoint in Phase 2 Golden-505
  - Phase 3 RESOLVE-IT is on going
Complete Resolution of NASH AND No Worsening of Fibrosis
Improvement in Fibrosis Stage AND No Worsening of NASH

GOLDEN 505-Peroxisome Proliferator-Activated Receptors (PPAR α/δ Pathways)
Elafibranor

RESOLVE-IT: Long-Term Evaluation of Elafibranor for NAS
Primary Endpoint at Year 1: Resolution of NASH no worsening fibrosis

Cenicriviroc: CENTAUR and NASH-AURORA studies

RESOLVE-IT: Long-Term Evaluation of Elafibranor for NAS
Primary Endpoint at Year 1: Resolution of NASH no worsening fibrosis

Placebo
Elafibranor 120 mg

N=144

OR (95% CI) 1.53 (0.70–3.34), P=0.28
OR (95% CI) 2.31 (1.02–5.24), P=0.045

≥2-Point Improvement in NAS AND No Worsening of Fibrosis

Placebo
Elafibranor 120 mg

Subjects, %

Participants

Year 1 Results

Placebo
CVC

CVC 150 mg QD
Placebo QD

Cenicriviroc: CENTAUR and NASH-AURORA studies

Selonsertib: Phase 2 and 3 Clinical Trials

STELLAR-4 Press Release:
“In the study of 877 enrolled patients who received study drug, 14.4% of patients treated with selonsertib 18 mg (p=0.56 vs. placebo) and 12.5% of patients treated with selonsertib 6 mg (p=1.00) achieved a ≥ 1-stage improvement in fibrosis according to the NASH Clinical Research Network (CRN) classification without worsening of NASH after 48 weeks of treatment, compared with 12.8% of patients who received placebo. Selonsertib was generally well-tolerated and safety results were consistent with prior studies.”

STELLAR-4 Press Release:
In the study of 802 enrolled and dosed patients, 9.3 percent of patients treated with selonsertib 18 mg (p=0.42 versus placebo) and 12.1 percent of patients treated with selonsertib 6 mg (p=0.93) achieved a ≥ 1-stage improvement in fibrosis according to the NASH Clinical Research Network (CRN) classification without worsening of NASH after 48 weeks of treatment, versus 13.2 percent with placebo. Selonsertib was generally well tolerated and safety results were consistent with prior studies.

N=72 patients 18–70 years of age who had either F2 or F3 confirmed by biopsy, mg or 18 mg of SEL alone, 6 mg or 18 mg of SEL + SIM, or 125 mg of SIM selonsertib; SIM, simzutumab
Obeticholic Acid: FLINT and REGENERATE Studies

Improvements in Histology over 72 Weeks

- **Obeticholic acid**
- **Placebo**

<table>
<thead>
<tr>
<th>Condition</th>
<th>Patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Histological Improvement</td>
<td>50</td>
</tr>
<tr>
<td>Resolution of fibrosis</td>
<td>30</td>
</tr>
<tr>
<td>Improvement in hepatocyte steatosis</td>
<td>40</td>
</tr>
<tr>
<td>Improvement in lobular steatosis</td>
<td>60</td>
</tr>
</tbody>
</table>

- *P* ≤0.001;  
- *P* < 0.05;  
- Resolution of NASH defined as not NAFLD or NAFLD but not NASH;  
- *P* < 0.01; N=219 adult patients with biopsy-confirmed NASH or borderline NASH and histological NAS of ≥4.

Positive Results from REGENERATE: A Phase 3 International, Randomized, Placebo-controlled Study Evaluating Obeticholic Acid Treatment for NASH

- OCA 25 mg met the primary endpoint of improvement in liver fibrosis with no worsening of NASH (p=0.0002* vs PBO)

- Antifibrotic effect of OCA: dose dependent and consistent across endpoints and key subgroups

- Although the additional primary endpoint of NASH resolution with no worsening of fibrosis was not met, OCA improved NASH disease activity based on several key histologic parameters including NAS, hepatocyte ballooning and inflammation

- AEs were mostly mild to moderate in severity and the most common were consistent with the known profile of OCA

*Statistically significant in accordance with the statistical analysis plan as agreed with the FDA. All other p values are nominal.
**Per protocol population with available fibrosis data at Month 18/EOT (n=656). Younossi Z, et al. EASL 2019, Vienna, Austria. #GS-06.
Fibroblast Growth Factor (FGF)19 and 21: Phase 2 Studies

**NGM 282 (FGF 19)**

- N=82 randomized
- 12 weeks duration  NAS > 4 allowed
- No cirrhosis

**Pegbelfermin (FGF 21) BMS-986036**

- N=74 randomized
- 16 weeks duration  NAS > 4 allowed
- No cirrhosis

FGF 19 and FGF 21 Improve NAFLD / NASH

Change in Absolute ALT

NGM282

Mean Change in Absolute ALT (IUL)
- Placebo
- 3 mg
- 6 mg

BMS PEG-FGF21

Mean Change in Absolute ALT (IUL)
- Placebo
- 10 mg QD
- 20 mg QW

>30% Relative Decrease in LFC

NGM282

% Pts with ≥30% Decrease in Relative LFC
- Placebo
- 3 mg
- 6 mg

BMS PEG-FGF21

% Pts with ≥30% Decrease in Relative LFC
- Placebo
- 10 mg QD
- 20 mg QW

Placebo Adjusted = -31 to -33 IU
Placebo Adjusted = -11 to -17 IU
Placebo Adjusted = 78% to 85%
Placebo Adjusted = 27% to 32%

Placebo adjusted rates provided as data were not a direct head to head trial comparison
Thyroid Receptor β Agonists for NAFLD / NASH

**Inclusion/exclusion**

- 2:1 MGL-3196 to PBO
- 125 patients enrolled in U.S.; 18 sites
- NASH on liver biopsy: NAS≥4 with F1–3
- ≥10% liver fat on MRI-PDFF
- Includes diabetics, statin therapy, representative NASH population

Resmetirom (MGL-3196): Phase 2 Results

- Week 36 vs placebo, resmetirom vs placebo
- More patients achieved a 2-point NAS improvement (56% vs 32%; \( P=.02 \))
- More patients achieved NASH resolution (27% vs 6%; \( P=.02 \))
- Reduced liver fat (MRI PDFF; \( P<.0001 \))
- Increased incidence of mild transient diarrhea with resmetirom occurred early in therapy

Future: Targeting Multiple Pathways Combinations with Complementary Mechanisms of Action

<table>
<thead>
<tr>
<th>Mechanism of Action</th>
<th>Disease Process/Pathway Target(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASK1 inhibitor (selonsertib) and non-steroidal FXR agonist (GS-9674) and/or ACC inhibitor (GS-0976)</td>
<td>Inflammation, fibrosis, and lipogenesis</td>
</tr>
<tr>
<td>Combined PPAR alpha and delta agonist (elafibranor) and an FXR agonist</td>
<td>Inflammation, fibrosis, and lipogenesis</td>
</tr>
<tr>
<td>Chemokine CCR2/CCR5 receptor blocker (cenicriviroc) in combination with a FXR agonist</td>
<td>Inflammatory and fibrosis</td>
</tr>
</tbody>
</table>

Combination of an apoptosis signal-regulating kinase (ASK1) inhibitor (selonsertib) with an acetyl-CoA carboxylase inhibitor (GS-0976) or a farnesoid X receptor agonist (GS-9674) in NASH

![Graph showing median relative change in MRI-PDFF](image)

ACC, acetyl-CoA carboxylase; ASK-1, apoptosis signal-regulating kinase 1; CCR, chemokine (C-C motif) receptor; FXR, farnesoid X receptor; MRI-PDFF, magnetic resonance imaging proton density fat fraction; NASH, non-alcoholic steatohepatitis; PPAR, peroxisome proliferator-activated receptor; SEL, selonsertib.

1. Lawitz E, et al. ILC. April 11-15, 2018; Paris, France. Abstract PS105;
3. Oseini AM, Sanyal AJ. Liver Int. 2017;37 Suppl. 1:97-103;
NAFLD and NASH are growing globally
NASH is predominantly progressive
Fibrosis is important predictor of long-term outcomes
Patients with NASH, especially those with fibrosis will need treatment and should be identified
Although liver biopsy is the current imperfect gold standard for NASH diagnosis, a number of non-invasive tests are being developed
Future management of NASH requires a multidisciplinary teams
Although a number drugs are being tested, only one drug has met phase 3 endpoint
Future therapies will require combination of different regimens

NASH: Current Approach and When Will New Treatment Options Be Available?
We acknowledge and thank AbbVie Inc. and Mallinckrodt Pharmaceuticals for providing educational grants to support this program.